SUPPLEMENTARY MATERIAL

Real-World Data Analysis of Second-Line Antiangiogenic Targeted Treatments Following Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies and First-Line FOLFOX for Patients with Metastatic Colorectal Cancer

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Table S1 Antitumor drugs recommended by the 2019 JSCCR guidelines for advanced CRC

Nonbiological		**Biological**		
Cytotoxic agents	**Other targeted treatment**	**Antiangiogenic drugs**	**Anti-EGFR monoclonal antibodies**	**Other targeted treatments**
• Fluoropyrimidines (capecitabine, 5-FU, S-1, UFT) • FTD/TPI monotherapy[a] • Irinotecan • Oxaliplatin	• Regorafenib	• Aflibercept beta • Bevacizumab • Ramucirumab	• Cetuximab • Panitumumab	• Pembrolizumab
Second-line irinotecan-based regimens including antiangiogenic drugs				
• FOLFIRI + bevacizumab • Irinotecan + S-1 + bevacizumab • Irinotecan + bevacizumab • CAPIRI + bevacizumab • FOLFIRI + ramucirumab • FOLFIRI + aflibercept beta				

5-FU fluorouracil, *CAPIRI* capecitabine + irinotecan, *CRC* colorectal cancer, *EGFR* epidermal growth factor receptor, *FOLFIRI* fluorouracil + irinotecan + leucovorin, *FTD/TPI* trifluridine/tipiracil, *JSCCR* Japanese Society for Cancer of the Colon and Rectum, *S-1* tegafur + gimestat + potassium otastat, *UFT* uracil + tegafur

[a]At the time the study was conducted

Table S2 Concomitant procedures and medications prescribed at baseline (before 1L therapy) and during 1L, 2L, and 3L therapy

Concomitant procedures and medications, *n* (%)	**Baseline[a] (*N* = 1163)**	**1L (*N* = 1163)**	**2L (*N* = 1163)**	**3L (*n* = 645)**
Proteinuria tests	650 (55.9)	546 (46.9)	876 (75.3)	381 (59.1)
NSAIDs	579 (49.8)	503 (43.3)	446 (38.3)	233 (36.1)
Antihypertensives	397 (34.1)	463 (39.8)	570 (49.0)	335 (51.9)
Topical steroids	190 (16.3)	1088 (93.6)	530 (45.6)	229 (35.5)
Minocycline	95 (8.2)	922 (79.3)	198 (17.0)	91 (14.1)
Magnesium sulfate injection	10 (0.9)	310 (26.7)	53 (4.6)	38 (5.9)

1L/2L/3L first-line/second-line/third-line, *NSAID* nonsteroidal anti-inflammatory drug
[a]Assessed within 60 days before the index date

Table S3 Subgroup Cox regression analysis of the factors associated with treatment duration from the start of 2L irinotecan-based chemotherapy plus any antiangiogenic drug in patients for whom total ADL and BMI were available (*n* = 528)

Covariate	HR	95% CI	*p*-value
Demographics and disease characteristics			
≥70 years at start of 2L therapy[a]	1.03	0.81, 1.31	0.78
Sex: male	1.01	0.79, 1.30	0.93
Left-sided CRC	0.81	0.61, 1.08	0.15
Metastases/comorbidities before starting 2L therapy[b]			
Liver metastases	0.98	0.78, 1.23	0.86
Lung metastases	0.94	0.72, 1.22	0.64
Diabetes	1.11	0.86, 1.44	0.41
Renal disease	1.10	0.76, 1.59	0.60
Liver disease	1.11	0.86, 1.43	0.43
Supportive medications before starting 2L therapy[b]			
NSAIDs[a]	1.25	0.99, 1.57	0.06
Antihypertensives[a]	1.20	0.95, 1.53	0.13
Prior antitumor therapies			
CRC surgery before index date	0.56	0.44, 0.72	<0.0001
CRC conversion surgery during 1L therapy	0.73	0.49, 1.09	0.13
Liver surgery during 1L therapy	0.65	0.35, 1.17	0.15
Duration of 1L therapy ≥6 months[a]	0.67	0.53, 0.83	<0.001
Additional clinical factors			
Total ADL independence	0.54	0.38, 0.76	<0.001
BMI ≤18.5 kg/m^2	1.17	0.87, 1.58	0.31

1L/2L first-line/second-line, *ADL* activities of daily living, *BMI* body mass index, *CI* confidence interval, *CRC* colorectal cancer, *HR* hazard ratio, *NSAID* nonsteroidal anti-inflammatory drug

[a]Within 60 days before starting 2L therapy, 37.9% (200/528) of patients were ≥70 years of age, 33.5% (177/528) of patients were prescribed NSAIDs, 33.9% (179/528) were prescribed antihypertensives, and 60.6% (320/528) had duration of 1L therapy ≥6 months

[b]Within 60 days before starting second-line therapy

Table S4 Five most common antiangiogenic and anti-EGFR antibody treatment regimens as 3L therapy

Patients, *N*	**3L antiangiogenic drug prescription (not FTD/TPI+BEV)**		**Patients, *N***	**3L anti-EGFR antibody prescription**	
	Treatment	***n* (%)**		**Treatment**	***n* (%)**
143	FOLFIRI, RAM	53 (37.1)	115	FOLFIRI, PANI	26 (22.6)
	FOLFIRI, AFL	19 (13.3)		IRI, CET	15 (13.0)
	IRIS, BEV	18 (12.6)		FOLFOX, PANI	14 (12.2)
	FOLFIRI, BEV	17 (11.9)		FOLFIRI, CET	13 (11.3)
	CAPOX, BEV	7 (4.9)		IRI, PANI	12 (10.4)

3L third-line, *AFL* aflibercept beta, *BEV* bevacizumab, *CAPOX* capecitabine + oxaliplatin, *CET* cetuximab, *EGFR* epidermal growth factor receptor, *FOLFIRI* leucovorin + 5-fluorouracil + irinotecan, *FOLFOX* leucovorin + 5-fluorouracil + oxaliplatin, *FTD/TPI* trifluridine/tipiracil, *IRIS* S-1 (tegafur + gimeracil + oteracil potassium) + irinotecan, *PANI* panitumumab, *RAM* ramucirumab

Table S5 Demographics and clinical characteristics of patients with CRC who started 3L therapy

Variable	3L therapy (*n* = 645)	3L treatment regimens					
		AA-based[a] (*n* = 143)	EGFRab-based (*n* = 115)	FTD/TPI (*n* = 144)	FTD/TPI+BEV (*n* = 129)	REG (*n* = 77)	Other (*n* = 37)
Number of hospital beds							
<200 beds	23 (3.6)	7 (4.9)	5 (4.3)	4 (2.8)	4 (3.1)	1 (1.3)	2 (5.4)
200–499 beds	369 (57.2)	81 (56.6)	63 (54.8)	90 (62.5)	67 (51.9)	44 (57.1)	24 (64.9)
≥500 beds	253 (39.2)	55 (38.5)	47 (40.9)	50 (34.7)	58 (45.0)	32 (41.6)	11 (29.7)
Designated cancer hospital	502 (77.8)	104 (72.7)	98 (85.2)	111 (77.1)	105 (81.4)	58 (75.3)	26 (70.3)
Demographics/disease characteristics							
Age, mean (SD)[b]	65.0 (10.9)	63.1 (11.7)	64.2 (10.9)	65.9 (10.3)	65.9 (10.2)	65.6 (11.9)	66.4 (8.5)
Sex: male	416 (64.5)	94 (65.7)	74 (64.3)	101 (70.1)	73 (56.6)	50 (64.9)	24 (64.9)
BMI, kg/m^2, mean (SD)[c]	22.4 (3.6)[d]	22.4 (4.2)[e]	22.5 (3.7)[f]	22.6 (3.2)[g]	21.3 (3.2)[h]	21.2 (3.6)[i]	22.7 (3.2)[j]
BMI ≤18.5 kg/m^2[c]	34 (14.6)[d]	10 (19.6)[e]	7 (14.9)[f]	4 (8.2)[g]	6 (14.0)[h]	6 (30.0)[i]	1 (4.3)[j]
ADL – independent[c]	193 (85.8)[k]	43 (89.6)[l]	40 (88.9)[m]	41 (85.4)[n]	33 (78.6)[o]	14 (73.7)[p]	22 (95.7)[q]
ADL – dependent[c]	32 (14.2)[k]	5 (10.4)[l]	5 (11.1)[m]	7 (14.6)[n]	9 (21.4)[o]	5 (26.3)[p]	1 (4.3)[q]
Left-sided CRC[r]	537 (83.3)	117 (81.8)	101 (87.8)	115 (79.9)	111 (86.0)	65 (84.4)	28 (75.7)
Right-sided CRC[r]	65 (10.1)	17 (11.9)	10 (8.7)	13 (9.0)	11 (8.5)	7 (9.1)	7 (18.9)
Antitumor therapies							
CRC surgery before index date	287 (44.5)	59 (41.3)	53 (46.1)	58 (40.3)	66 (51.2)	30 (39.0)	21 (56.8)
CRC conversion surgery during 1L or 2L therapy	72 (11.2)	17 (11.9)	20 (17.4)	15 (10.4)	7 (5.4)	6 (7.8)	7 (18.9)
Liver surgery during 1L or 2L therapy	47 (7.3)	12 (8.4)	20 (17.4)	4 (2.8)	7 (5.4)	1 (1.3)	3 (8.1)
Lung surgery during 1L or 2L therapy	3 (0.5)	1 (0.7)	1 (0.9)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Duration of therapy from 1L to start of 3L, mean, months (SD)	18.9 (9.2)	17.1 (8.7)	18.9 (8.9)	19.3 (9.0)	20.9 (9.3)	18.6 (9.0)	18.0 (11.2)
Sites of metastasis[c]							
Liver	419 (65.0)	84 (58.7)	81 (70.4)	95 (66.0)	88 (68.2)	49 (63.6)	22 (59.5)
Lung	151 (23.4)	26 (18.2)	24 (20.9)	39 (27.1)	40 (31.0)	18 (23.4)	4 (10.8)
Bone	49 (7.6)	11 (7.7)	9 (7.8)	12 (8.3)	8 (6.2)	6 (7.8)	3 (8.1)
Brain	8 (1.2)	3 (2.1)	1 (0.9)	1 (0.7)	3 (2.3)	0 (0.0)	0 (0.0)
Comorbidities[c]							
Hypertension	341 (52.9)	69 (48.3)	60 (52.2)	79 (54.9)	77 (59.7)	37 (48.1)	19 (51.4)
Diabetes	174 (27.0)	37 (25.9)	39 (33.9)	41 (28.5)	30 (23.3)	18 (23.4)	9 (24.3)
Liver disease	174 (27.0)	34 (23.8)	35 (30.4)	42 (29.2)	37 (28.7)	16 (20.8)	10 (27.0)
Renal disease	87 (13.5)	18 (12.6)	16 (13.9)	18 (12.5)	18 (14.0)	13 (16.9)	4 (10.8)
Dry skin/itching	519 (80.5)	116 (81.1)	94 (81.7)	112 (77.8)	112 (86.8)	59 (76.6)	26 (70.3)
Rash/acne	185 (28.7)	49 (34.3)	34 (29.6)	42 (29.2)	31 (24.0)	19 (24.7)	10 (27.0)
Paronychia	42 (6.5)	12 (8.4)	11 (9.6)	8 (5.6)	8 (6.2)	3 (3.9)	0 (0.0)
Neuropathy	155 (24.0)	39 (27.3)	25 (21.7)	36 (25.0)	33 (25.6)	13 (16.9)	9 (24.3)

All values are *n* (%) unless indicated otherwise

1L/2L/3L first-line/second-line/third-line, *AA* antiangiogenic, *ADL* activities of daily living, *BEV* bevacizumab, *BMI* body mass index, *CRC* colorectal cancer, *EGFRab* epidermal growth factor receptor antibody, *FTD/TPI* trifluridine/tipiracil, *REG* regorafenib, *SD* standard deviation

[a]Not FTD/TPI+BEV; [b]At start of third-line therapy; [c]Assessed within 60 days before starting third-line therapy; [d]*N* = 233; [e]*N* = 51; [f]*N* = 47; [g]*N* = 49; [h]*N* = 43; [i]*N* = 20; [j]*N* = 23; [k]*N* = 225; [l]*N* = 48; [m]*N* = 45; [n]*N* = 48; [o]*N* = 42; [p]*N* = 19; [q]*N* = 23; [r]Assessed within 60 days before the index date for first-line therapy

Table S6 Demographics and clinical characteristics of the subgroup of patients with left-sided CRC

Variable	Start of 1L therapy (*N* = 970)	Start of 2L therapy (*N* = 970)	Start of 2L therapy		
			Bevacizumab (*n* = 605)	Ramucirumab (*n* = 269)	Aflibercept beta (*n* = 96)
Number of hospital beds					
<200 beds	38 (3.9)		26 (4.3)	11 (4.1)	1 (1.0)
200–499 beds	541 (55.8)		333 (55.0)	162 (60.2)	46 (47.9)
≥500 beds	391 (40.3)		246 (40.7)	96 (35.7)	49 (51.0)
Designated cancer hospital	768 (79.2)		468 (77.4)	216 (80.3)	84 (87.5)
Demographics/disease characteristics					
Sex: male	668 (68.9)		412 (68.1)	185 (68.8)	71 (74.0)
Age, years, mean (SD)	63.7 (10.5)	64.6 (10.5)[a]	64.6 (10.5)[a]	64.5 (10.3)[a]	64.3 (11.4)[a]
BMI, kg/m^2, mean (SD)[b]	22.0 (3.5)[c]	21.9 (3.8)[d]	22.1 (3.9)[e]	21.7 (3.3)[f]	21.5 (3.9)[g]
BMI ≤18.5 kg/m^2[b]	111 (13.0)[c]	82 (18.5)[d]	47 (16.4)[e]	23 (20.7)[f]	12 (26.7)[g]
ADL – independent[b]	781 (93.2)[h]	392 (89.7)[i]	251 (89.3)[j]	102 (92.7)[k]	39 (84.8)[l]
ADL – dependent[b]	57 (6.8)[h]	45 (10.3)[i]	30 (10.7)[j]	8 (7.3)[k]	7 (15.2)[l]
Antitumor therapies					
CRC surgery before index date	407 (42.0)	-	240 (39.7)	124 (46.1)	43 (44.8)
CRC conversion surgery during 1L therapy	-	101 (10.4)	65 (10.7)	24 (8.9)	12 (12.5)
Liver surgery during 1L therapy	-	62 (6.4)	32 (5.3)	23 (8.6)	7 (7.3)
Lung surgery during 1L therapy	-	4 (0.4)	2 (0.3)	2 (0.7)	0 (0)
Duration of 1L therapy, mean, months (SD)	-	9.81 (6.86)	9.75 (6.89)	9.92 (7.03)	9.93 (6.29)
Sites of metastasis[b]					
Liver	605 (62.4)	623 (64.2)	392 (64.8)	166 (91.7)	65 (67.7)
Lung	172 (17.7)	209 (21.5)	128 (21.2)	64 (23.8)	17 (17.7)
Bone	41 (4.2)	64 (6.6)	40 (6.6)	19 (7.1)	5 (5.2)
Brain	6 (0.6)	7 (0.7)	6 (1.0)	0 (0)	1 (1.0)
Comorbidities[b]					
Hypertension	297 (30.6)	361 (37.2)	219 (36.2)	99 (36.8)	43 (44.8)
Diabetes	240 (24.7)	259 (26.7)	154 (24.5)	77 (28.6)	28 (29.2)
Liver disease	174 (17.9)	241 (24.8)	142 (23.5)	72 (26.8)	27 (28.1)
Renal disease	87 (9.0)	91 (9.4)	47 (7.8)	33 (12.3)	11 (11.5)
Dry skin/itching	265 (27.3)	775 (79.9)	483 (79.8)	211 (78.4)	81 (84.4)
Rash/acne	69 (7.1)	318 (32.8)	203 (33.6)	90 (33.5)	25 (26.0)
Paronychia	3 (0.3)	78 (8.0)	47 (7.8)	26 (9.7)	5 (5.2)
Neuropathy	48 (4.9)	189 (19.5)	115 (19.0)	50 (18.6)	24 (25.0)

All values are *n* (%) unless indicated otherwise

1L/2L first-line/second-line, *ADL* activities of daily living, *BMI* body mass index, *CRC* colorectal cancer, *SD* standard deviation

[a]Assessed at the start of second-line therapy; [b]Assessed within 60 days before the index date for first-line therapy and within 60 days before starting second-line therapy for second-line therapy; [c]*N* = 851; [d]*N* = 443; [e]*N* = 287; [f]*N* = 111; [g]*N* = 45; [h]*N* = 838; [i]*N* = 437; [j]*N* = 281; [k]*N* = 110; [l]*N* = 46

Table S7 Cox regression analysis of the factors associated with treatment duration from the start of 2L irinotecan-based chemotherapy plus any antiangiogenic drug in the subgroup of patients with left-sided CRC (*n* = 970)

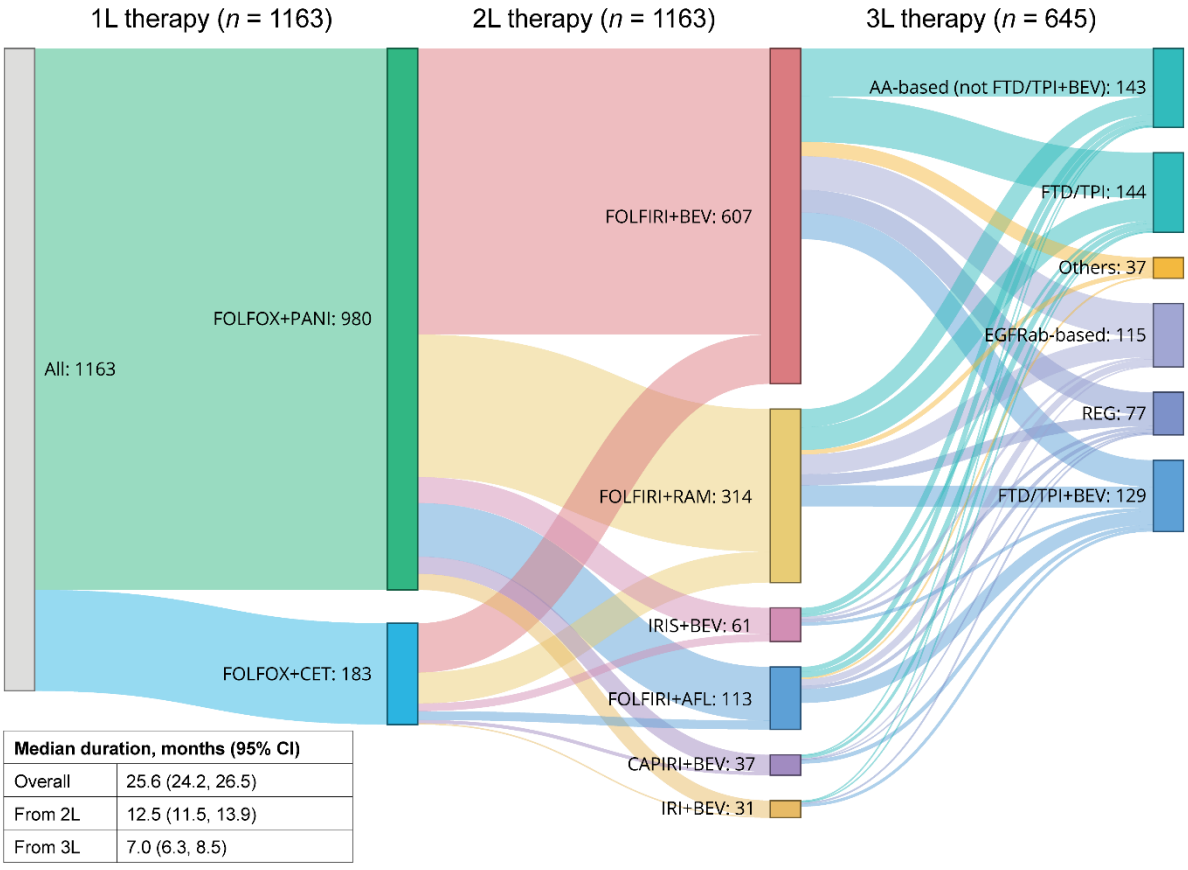
Covariate	HR	95% CI	*p*-value
Demographics and disease characteristics			
≥70 years at start of 2L therapy[a]	1.12	0.94, 1.35	0.20
Sex: male	1.09	0.91, 1.31	0.36
Metastases/comorbidities before starting 2L therapy[b]			
Liver metastases	1.10	0.92, 1.32	0.28
Lung metastases	0.96	0.78, 1.18	0.68
Diabetes	1.04	0.86, 1.26	0.69
Renal disease	1.18	0.89, 1.58	0.25
Liver disease	0.98	0.81, 1.19	0.84
Supportive medications before starting 2L therapy[b]			
NSAIDs[a]	1.28	1.06, 1.54	0.01
Antihypertensives[a]	1.17	0.97, 1.43	0.10
Prior antitumor therapies			
CRC surgery before index date	0.60	0.50, 0.72	<0.001
CRC conversion surgery during 1L therapy	0.96	0.72, 1.27	0.76
Liver surgery during 1L therapy	0.63	0.42, 0.93	0.02
Duration of 1L therapy ≥6 months[a]	0.80	0.67, 0.95	0.01

1L/2L first-line/second-line, *CI* confidence interval, *CRC* colorectal cancer, *HR* hazard ratio, *NSAID* nonsteroidal anti-inflammatory drug

[a]Within 60 days before starting 2L therapy, 35.9% (348/970) of patients were ≥70 years of age, 26.3% (255/970) of patients were prescribed NSAIDs, 28.9% (280/970) were prescribed antihypertensives, and 68.1% (661/970) had duration of 1L therapy ≥6 months

[b]Within 60 days before starting 2L therapy

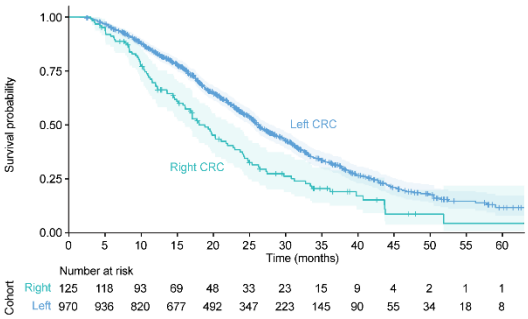
Fig. S1 Treatment sequences and median duration for 1L FOLFOX plus anti-EGFR antibody therapy, 2L irinotecan-based chemotherapy plus any antiangiogenic drug, and 3L therapy with any treatment regimen. *1L/2L/3L* first-line/second-line/third-line, *AA* antiangiogenic, *AFL* aflibercept beta, *BEV* bevacizumab, *CAPIRI* irinotecan + capecitabine, *CET* cetuximab, *CI* confidence interval, *EGFRab* epidermal growth factor receptor monoclonal antibody, *FOLFIRI* leucovorin + 5-fluorouracil + irinotecan, *FOLFOX* leucovorin + 5-fluorouracil + oxaliplatin, *FTD/TPI* trifluridine/tipiracil, *IRI* irinotecan, *IRIS* irinotecan + tegafur + gimeracil + oteracil potassium, *PANI* panitumumab, *RAM* ramucirumab, *REG* regorafenib



Median duration, months (95% CI)	
Overall	25.6 (24.2, 26.5)
From 2L	12.5 (11.5, 13.9)
From 3L	7.0 (6.3, 8.5)

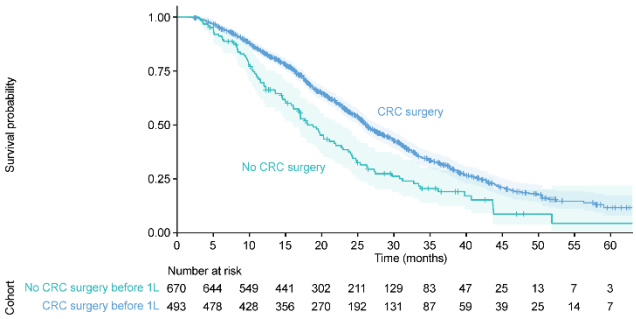
Fig. S2 Median overall treatment duration by CRC sidedness (**a**) and CRC surgery before starting 1L therapy (**b**). *1L* first-line, *CI* confidence interval, *CRC* colorectal cancer

a



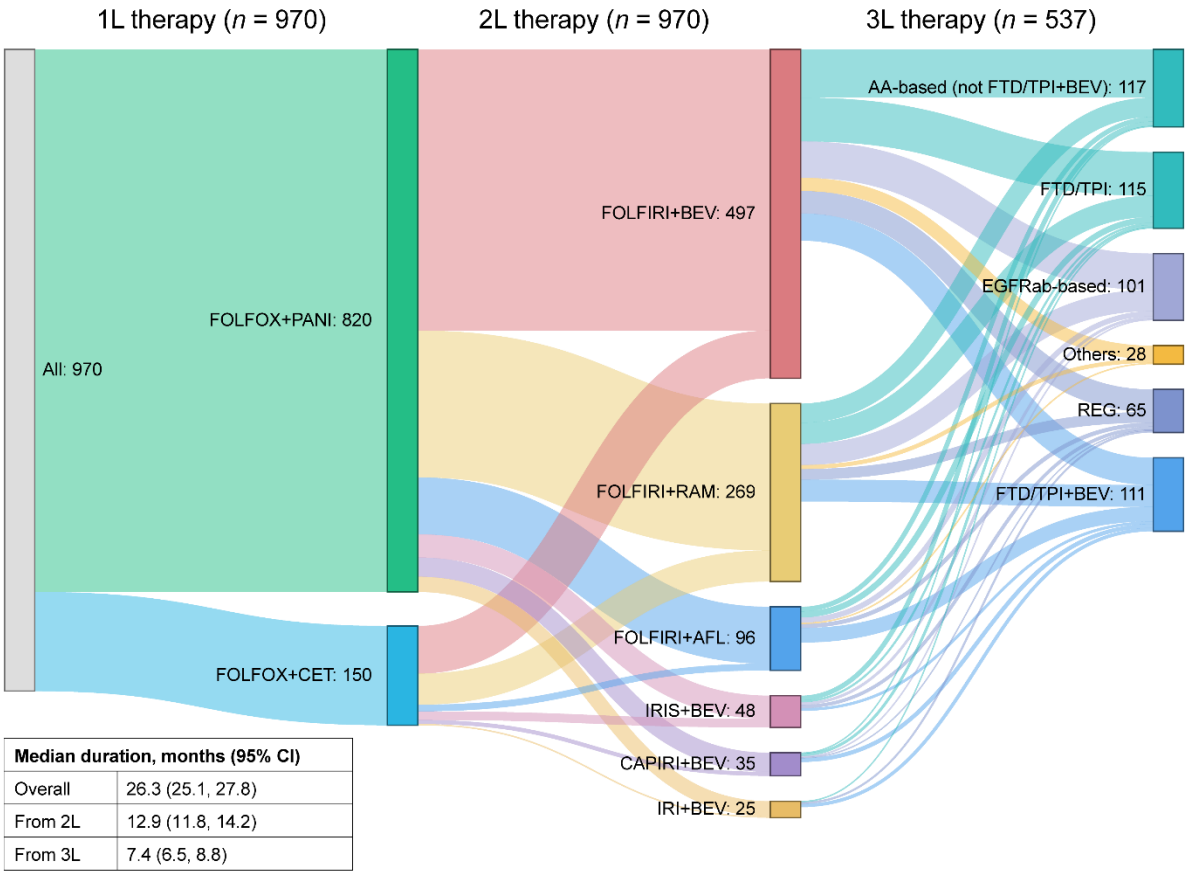
Treatment duration	*N*	Median, months (95% CI)
Left CRC	970	26.3 (25.1, 27.8)
Right CRC	125	18.8 (16.1, 22.8)

b



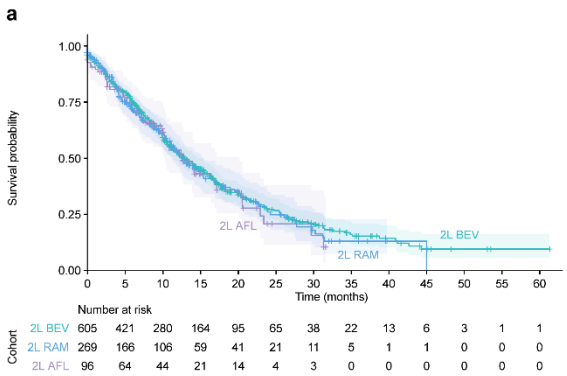
Treatment duration	*N*	Median, months (95% CI)
CRC surgery	493	29.3 (27.3, 31.9)
No CRC surgery	670	23.0 (21.8, 24.8)

Fig. S3 Treatment sequences and median duration for 1L FOLFOX plus anti-EGFR antibody therapy, 2L irinotecan-based chemotherapy plus any antiangiogenic drug, and 3L therapy with any treatment regimen for the subgroup of patients with left-sided CRC. *1L/2L/3L* first-line/second-line/third-line, *AA* antiangiogenic, *AFL* aflibercept beta, *BEV* bevacizumab, *CAPIRI* irinotecan + capecitabine, *CET* cetuximab, *CI* confidence interval, *CRC*, colorectal cancer, *EGFRab* epidermal growth factor receptor monoclonal antibody, *FOLFIRI* leucovorin + 5-fluorouracil + irinotecan, *FOLFOX* leucovorin + 5-fluorouracil + oxaliplatin, *FTD/TPI* trifluridine/tipiracil, *IRI* irinotecan, *IRIS* irinotecan + tegafur + gimeracil + oteracil potassium, *PANI* panitumumab, *RAM* ramucirumab, *REG* regorafenib

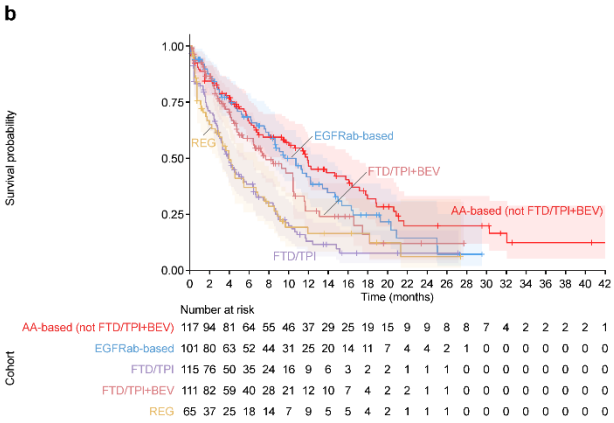


Median duration, months (95% CI)	
Overall	26.3 (25.1, 27.8)
From 2L	12.9 (11.8, 14.2)
From 3L	7.4 (6.5, 8.8)

Fig. S4 Treatment duration from the start of 2L irinotecan-based chemotherapy plus any antiangiogenic drug for the subgroup of patients with left-sided CRC (**a**) and from the start of 3L therapy (**b**) for the subgroup of patients with left-sided CRC by treatment regimens. *2L/3L* second-line/third-line, *AA* antiangiogenic, *AFL* aflibercept beta, *BEV* bevacizumab, *CI* confidence interval, *EGFRab* epidermal growth factor receptor monoclonal antibody, *FTD/TPI* trifluridine/tipiracil, *RAM* ramucirumab, *REG* regorafenib



Treatment duration	*N*	Median, months (95% CI)
2L BEV	605	13.0 (11.5, 14.7)
2L RAM	269	12.8 (11.2, 15.4)
2L AFL	96	12.8 (10.4, 20.2)



Treatment duration	*N*	Median, months (95% CI)
AA-based (not FTD/TPI+BEV)	117	12.0 (9.4, 16.5)
EGFRab-based	101	9.7 (8.2, 13.5)
FTD/TPI+BEV	111	7.8 (5.4, 10.5)
FTD/TPI	115	3.9 (3.2, 5.8)
REG	65	4.0 (3.0, 6.9)